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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/642,468	08/15/2003	Zhuyin Li	USAV2002/0098USNP	3125

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 03/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/642,468	LI ET AL.	
	Examiner	Art Unit	
	Mohammad Meah	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,13-16,22-26 and 28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,13-16,22-26 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/5/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant, on date 1/05/2006 elected with traverse Group II (claims 1, 4-8, 13-16, 22-26 and 28-32) for examination.

Election/Restriction

Applicant, on date 1/05/2006 elected with traverse Group II (claims 1, 4-8, 13-16, 22-26 and 28-32), drawn to method of screening compound or agent that decrease activities of prostaglandin E synthesase comprising amino acid sequence of SEQ ID NO: 4 for examination.

Applicant's election with traverse of Group II (claims 1, 4-8, 13-16, 22-26 and 28-32) in the reply filed on 1/05/2006 is acknowledged.

The traversal is on the ground(s) that group I (claims 1-3, 6-12, 16-21 and 27) and Group II (claims 1, 4-8, 13-16, 22-26 and 28-32) inventions are not independent because they involve two different species SEQ ID NO: 2 and 4. Applicants argument for considering SEQ ID NO: 2 and 4 as two different species in the method step was found persuasive and prostaglandin E synthase comprising SEQ ID NO: 2 and prostaglandin D synthase comprising SEQ ID NO: 4 will be considered as two species. However restriction requirement between the species still remains.

Claim 1, 6-8, 16, 29 and 32 link(s) inventions I and II. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise requiring all the

limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 Claims that require all the limitations of an allowable linking claim will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim(s) including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Applicants further argue that there would be no undue burden on the examiner to examine claims directed to group I and group II. This is not persuasive because while the search for each of these distinct groups would be overlapping it would not be coextensive. Art that applies for ProstglandinE synthase of SEQ ID NO: 2 and prostaglandinD synthase of SEQ ID NO: 4. may or may not be relevant to the others. Therefore the restriction is maintained and FINAL.

Claims 2-3, 9-12, 17-21 and 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/05/2006.

Priority

Acknowledgement is made of applicant's PCT priority date based on application filing date of 03/06/2001 in GB # PCT/GB01/00949.

35 U.S.C 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, 4, 7-8, 13-16, 25, 29-32 are rejected under U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor at the time the application was filed, had possession of the claimed invention.

These claims are directed to methods of determining agent that decrease the activity of prostaglandin synthase by measuring fluorescence using any substrate, any prostaglandin synthase or any prostaglandin D synthase, any cofactor and any fluorescence label. Furthermore these claims are directed to a genus of prostaglandin

synthase from any source. The specification teaches the structure of only two representative species of such prostaglandin synthase (prostaglandin E synthase of SEQ ID NO: 2 or prostaglandin D synthase of SEQ ID NO: 4. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of prostaglandin synthase. The specification fails to describe in any fashion the physical and/or chemical properties of the claimed class of prostaglandin synthases,cofactors, substrates and fluorescence labels. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1, 4, 7-8, 13-16, 25, 29-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of determining agent that decrease the activity of prostaglandin D synthase comprising amino acid sequence of SEQ ID NO:4 by measuring fluorescence using Texas Red (TR) as fluorescence label, does not reasonably provide enablement for methods of determining agent that decrease the activity of any prostaglandin synthase by measuring fluorescence using any substrate, any cofactor and any fluorescence label. The claims broadly recite the use of **any** substrate and **any** fluorescence label. The specification fails to describe how to label (or conjugate) any substrate with any fluorescence label and measure fluorescence using any label and any agent. The specification fails to describe in any fashion the physical and/or chemical properties of

the claimed class of substrates and labels as discussed above. As the structure of the claimed substances are not defined in any way, one of ordinary skill in the art would not be able to make and use any such labeled substrate without undue experimentation to first find out how to conjugate the substrate with the labels (as method of conjugation requires prior knowledge of the structure and function of both the substrate and labels). Furthermore, the claimed class of compounds is likely to include many compounds, which one of ordinary skill in the art would be unable to make and use without undue experimentation.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of methods of determining agent that decrease the activity of any Prostaglandin synthase by measuring fluorescence using any substrate and any fluorescence label. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of substances having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claims 1-2, 4, 7-8, 11, 13-16, 25, 29-32 broadly recite method of detecting agents that inhibit any prostaglandin synthase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of prostaglandin synthase polypeptide broadly encompassed by the methods of the claims. Since the amino acid sequence of a protein determines its

structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only two prostaglandin synthase polypeptides.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass methods of using any prostaglandin synthase because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting prostaglandin synthase activity; (B) the general tolerance of prostaglandin synthase polypeptide activities to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any prostaglandin synthase polypeptide residues with an expectation of obtaining the desired biological function; and (D) the

specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of using prostaglandin synthase polypeptides with an enormous number of amino acid modifications of the protein of SEQ ID NO: 2 or 4. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of prostaglandin synthase polypeptides for the use in the claimed methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-5, 7, 14 and 29-30 are rejected under 35 U.S.C. 103(a) by Van dyke et al. Clin. Chem. 1979, vol. 25, pp 1655-61) or Brennecke et al. (prostaglandins 1982, vol. 8, pp 615-34) or Kanaoka et al. (Eur. J. Biochem. 2000, 267, 3315-3322) in view of Kirkemo et al. (US PAT4510251).

Applicant's method of measurement of the activity of prostaglandin synthase is based on measuring the amount of prostaglandin produced (enzyme reaction product) by fluorescence polarization technique.

Claims 1, 7,14 and 29-32 are drawn to a method of detection of agent that decrease the activity of prostaglandin synthase comprising measuring fluorescence of a mixture of prostaglandin labeled with fluorescent label and antibody using fluorescence polarization technique in the presence and absence of other agent(s).

Claims 4-5 are drawn to a method of detection of agent that decrease the activity of hematopoietic prostaglandin D synthase (hPGDS, claim 4) or hPGDS comprising amino acid sequence of SEQ ID NO: 4 (claim 5) comprising measuring fluorescence of a mixture of prostaglandin labeled with fluorescent label and antibody using fluorescence polarization technique in the presence and absence of other agent(s).

Each of Brennecke et al. (prostaglandins 1982, vol. 8, pp 615-34) and Van dyke et al. teaches radioimmunoassay technique to identify the agents that inhibit prostaglandin synthase by measuring prostaglandin produced by the prostaglandin synthase.

Furthermore, Brennecke et al. teaches radioimmunoassay technique to identify the agents that inhibit prostaglandin synthase in presences of glutathione cofactor by measuring prostaglandin produced by the prostaglandin synthase.

Kanaoka et al. teach spectrophotometric technique to measure the activity of hPGDS, which has 100% sequence identity with SEQ ID NO: 4 of the present application, in presences of glutathione cofactor by measuring prostaglandin produced by the said hPGDS.

Kirkemo et al. (US PAT4510251) teach fluorescence polarization technique to detect agent or ligand (such as prostaglandin) in biological fluid comprising mixing a solution of variety of ligands (including prostaglandin) labeled with fluorescence labels (such as fluorescin) and an antibody thereto. Unlabeled prostaglandin in the biological fluid and the fluorescenctly labeled prostaglandin compete for the antibody forming prostaglandin-antibody and fluorescin –labeled prostaglandin-antibody complex such that the amount of labeled complex is lowered in the proportion to the amount of prostaglandin in the biological fluid. Fluorescence polarization technique is used to measure fluorescin /antibody/prostaglandin mixture and compared with labels/prostaglandin (control) to quantify the prostaglandin in the sample.

It is well known in prior art that fluorescence polarization can be performed much more simply and efficiently than radioimmunoassay technique.

As such it would have been obvious to one of ordinary skill in the art to use fluorescence polarization technique as taught by Kirkemo et al. (US PAT4510251) to

measure the amount of prostaglandin produced by the prostaglandin synthase and correlate it to an agent that inhibit prostaglandin synthase as taught by Van dyke et al. Clin. Chem. 1979, vol. 25, pp 1655-61) or Brennecke et al (prostaglandins 1982, vol. 8, pp 615-34) or Kanaoka et al. (Eur. J. Biochem. 2000, 267, 3315-3322).

Claim 8, 15-16, 22, 28, 31-32 rejected under 35 U.S.C. 103(a) by Van dyke et al. (Clin. Chem. 1979, vol. 25, pp 1655-61), Brennecke et al. (prostaglandins 1982, vol. 8, pp 615-34) or Kanaoka et al. ((Eur. J. Biochem. 2000, 267, 3315-3322) in view of Kirkemo et al. (US PAT4510251) as unpatentable as applied to claims 1, 4, 7,14 and 29-30 above, and further in view of Roederer et al. (US PAT 5714386) and Arakawa et al. (J. Pharm.and Biomed Anal. 1997, 15, pp 1537-1544).

Claims 8, 15-16, 22, 28, 31-32 are drawn to a method of detection of agent that decrease the activity of prostaglandin synthase comprising using fluorescence polarization technique using Texas red conjugated to prostaglandin and an antibody thereto in the presence and absence of other agent(s).

Roederer et al. (US PAT 5714386) teach conjugation of variety of fluorescence labels (including Texas red) to substrates or ligands of protein (including conjugation of Texas red to prostaglandin) and use the said fluorescence label for fluorescence immunoassay.

Arakawa et al. teach Taxes red labeled DNA primer and use Laser induced fluorescence technique to detect point mutation in genomic DNA illuminating the

analyte at 594 nm and measuring it at 615 nm (usual excitation and emission wave length of Texas red) wave length.

As such it would have been obvious to one of ordinary skill in the art to use Texas red conjugated to prostaglandin as suggested by Roederer et al. and use 594 nm exitation wavelength and 615 nm (usual excitation and emission wave length of Texas red) as detection wave length as suggested by Arakawa et al. and use it in fluorescence polarization technique as taught by the combination of Roederer et al. and Kirkemo et al. (US PAT4510251) to measure prostaglandin that produce by the prostaglandin synthase and correlate it to an agent that inhibit prostaglandin synthase as taught by Brennecke et al. as discussed above.

Claim 6, 13, 23-24, 28, are rejected under 35 U.S.C. 103(a) by Van dyke et al. Clin. Chem. 1979, vol. 25, pp 1655-61), Brennecke et al. (prostaglandins 1982, vol. 8, pp 615-34) or Kanaoka et al., Roederer et al. (US PAT 5714386) and Arakawa et al. (J. Pharm.and Biomed Anal. 1997, 15, pp 1537-1544) in view of Kirkemo et al. (US PAT4510251) as unpatentable as applied to claims 1, 4, 7-8,14-16, 22 and 29-32 above, and further in view of Murakami et al. (J. Biol. Chem. 2000, vol. 275, pp 32783-32792).

Claims 6, 13, 23-25, 28, are drawn to a method of detection of agent that decrease the activity of prostaglandin synthase comprising using fluorescence polarization technique using Texas red conjugated to prostaglandin and an antibody thereto using of $FeCl_2$ as a stop solution for the prostaglandin synthase reaction.

Murakami et al. teach the use of of $FeCl_2$ to stop PGH_2 to PGE_2 convertion during the measurement of prostaglandin synthase activity.

As such it would have been obvious to one of ordinary skill in the art to use $FeCl_2$ to stop the PGH_2 to PGE_2 or PGD_2 convertion as suggested by Murakami et al. and use it in fluorescence polarization technique in combination of Brennecke et al. (prostaglandins 1982, vol. 8, pp 615-34) or Kanaoka et al., Roederer et al. (US PAT 5714386), Arakawa et al. (J. Pharm.and Biomed Anal. 1997, 15, pp 1537-1544) and Kirkemo et al. (US PAT4510251) to measure prostaglandin that produce by the prostaglandin synthase and correlate it to an agent that inhibit prostaglandin synthase as taught by Brennecke et al. as discussed above.

Claims 25-26 are rejected under 35 U.S.C. 103(a) by Van dyke et al. Clin. Chem. 1979, vol. 25, pp 1655-61), Brennecke et al. (prostaglandins 1982, vol. 8, pp 615-34) or Kanaoka et al., Roederer et al. (US PAT 5714386) and Arakawa et al. (J. Pharm.and Biomed Anal. 1997, 15, pp 1537-1544), Murakami et al. (J. Biol. Chem. 2000, vol. 275, pp 32783-32792) in view of Kirkemo et al. (US PAT4510251) as unpatentable as applied to claims 1, 4, 6-8,14-13, 22-24 and 28-32 above, and further in view Gupta et al. (US PAT 5272257).

Claims 25-26 are drawn to a method of detection of agent that decrease the activity of prostaglandin synthase comprising using fluorescence polarization technique

using Texas red conjugated to prostaglandin by a linker and an antibody thereto using of $FeCl_2$ as a stop solution for the prostaglandin synthase reaction.

Gupta et al. teaches the conjugation of substrate with texas red using a succinimidyl ester linker.

As such it would have been obvious to one of ordinary skill in the art to use succimidyl ester or carboduimide as a linker to conjugate prostaglandin with texas red as suggested by Gupta et al. and use it in fluorescence polarization technique as suggested by the combination of Brennecke et al. (prostaglandins 1982, vol. 8, pp 615-34) or Kanaoka et al., Roederer et al. (US PAT 5714386) and Arakawa et al. (J. Pharm.and Biomed Anal. 1997, 15, pp 1537-1544), Murakami et al. (J. Biol. Chem. 2000, vol. 275, pp 32783-32792) and Kirkemo et al. (US PAT4510251) to measure prostaglandin that produce by the prostaglandin synthase and correlate it to an agent that inhibit prostaglandin synthase as taught by Brennecke et al. as discussed above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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